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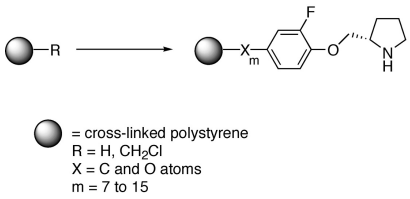

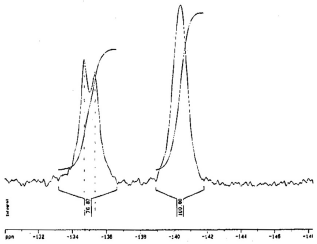

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Development of Cross-Linked Polystyrene-Supported Chiral Amines Featuring a Fluorinated Linker for Gel-Phase ^{19}F NMR Spectrometry Monitoring of Reactions

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Ten cross-linked polystyrene-supported, protected chiral amines featuring both a spacer, comprising from 5 to 15 atoms, and a fluorinated linker have been successfully prepared. The development of the monitoring technique by gel-phase ^{19}F NMR spectrometry on cross-linked polystyrene derivatives proved to be of high value in four steps of the process, as shown by the comparison of data gathered from both a classic NMR spectrometer and elemental analysis. Gel-phase ^{19}F NMR spectrometry, thus, constitutes a useful technique that complements IR and ^{13}C NMR spectrometries for the qualitative monitoring of reactions. In addition, quantitative determination of the conversion in a given transformation is possible, provided that ^{19}F chemical shifts of the substrate and the product be different enough ($\Delta\delta >$ base width), as illustrated by the Mitsunobu coupling process (**16** → **17**). The technique is nondestructive, and the samples used to monitor the reactions may be returned to the reaction medium. Deprotection of the above amines was achieved and furnished eight of the final resins in good to acceptable purity for future applications.

Introduction

The explosive development of nonpeptidic, supported organic chemistry during the past decade has been largely due to the need of pharmaceutical and agrochemical companies, for instance, to produce great numbers of new molecular entities for large-scale screening. Supported chemistry is, indeed, well-suited for automation, and this formed the basis for the development of the very concepts of combinatorial and parallel syntheses, as well as for the production of libraries.[1]

A drawback of cross-linked polystyrene-supported chemistry is the relative lack of analytical, nondestructive methods to monitor reactions and assess conversions of substrates into products. Several techniques, such as high-resolution magic angle spinning nuclear magnetic resonance (HRMAS NMR) spectrometry or presaturation of the polymeric backbone signals, for example, have thus emerged to try to overcome these difficulties.[2,3] However, these techniques either require specific instrumentation or are time-consuming, thus leaving room for the development of alternatives.

Among the possibilies is the use of standard, gel-phase NMR spectrometry. However, the only nuclei leading to relatively well resolved gel-phase NMR spectra are ^{13}C, ^{15}N, ^{19}F, and ^{31}P because their strong chemical shift dispersion partly solves the problems of chemical shift anisotropy and dipolar coupling.[4] Among these nuclei, ^{19}F represents a candidate of choice to be incorporated in a linker because of both the large number of commercially available fluorinated molecules and the fact that polymers are usually devoid of fluorine, and will, thus, not interfere in the analysis. In addition, ^{19}F features a natural abundance of 100% and a high relative intensity of 0.83 (compared to ^{1}H).

The literature reports several examples of fluorine-bearing substrates grafted on polymers (cross-linked polystyrene (PS) and polystyrene cross-linked poly(ethylene glycol) graft polymers (PS−PEG)) and the use of gel-phase ^{19}F NMR spectrometry to monitor their reactions.[5] Expectedly, the resolution of ^{19}F NMR spectra of PS−PEG-supported materials was found to be markedly higher than those of PS-supported substrates/products.

To our knowledge, only four reports on fluorinated linkers, with the aim of using ^{19}F NMR spectrometry to monitor reactions, have been published so far. In all cases, a PS−PEG support was used, and the resolution of the spectra was shown to be close to that of solution-phase spectra.[6] In addition, one paper reports on the use of a fluorinated cross-linked chloromethylpolystyrene to monitor reactions involving fluorinated reactants.[7] No report exists, however, on the use of a fluorinated linker grafted on cross-linked polystyrene, despite the fact that the analytical problem is most crucial in this case. In the course of a study on the use of PS-supported chiral amines in various organochemical transformations, we produced several new PS resins bearing in some cases a spacer and a fluorinated linker. We hereafter

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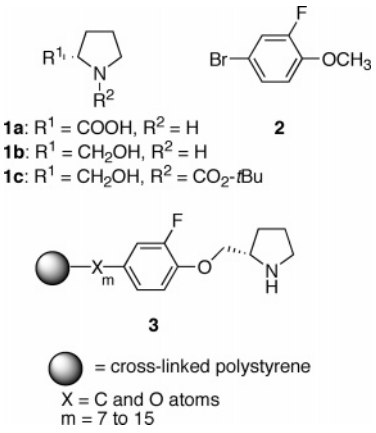


Figure 1. Structures of compounds **1** and **2** and generic structure of supported prolinol derivatives **3**.

report on their synthesis as well as on the influence of several parameters on the resolution of gel-phase ^{19}F NMR spectra of the various intermediates and show that gel-phase ^{19}F NMR spectrometry constitutes an adequate means of monitoring reactions.

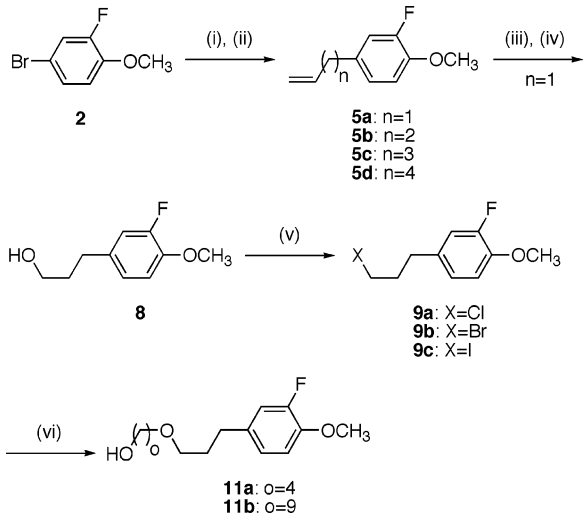
Results and Discussion

The ready availability of both enantiomers of proline **1a**, the presence of an additional function group to tether the molecule to the polymer, and the numerous involvement of derivatives of these amines in efficient solution-phase asymmetric synthesis, guided us in the choice of (*S*)-(−)-prolinol (**1b**) as the starting chiral secondary amine (Figure 1).[8,9] Among the possible precursors of the fluorinated linker, we selected the commercially available 4-bromo-2-fluoroanisole (**2**). Indeed, the inherent inertness of the aryl group warrants the stability and lack of reactivity of the linker under a variety of experimental conditions. In addition, the presence of both the bromine atom and the ether group allowed us to envision a smooth grafting of the amine unit by transforming the ether moiety, as well as the tethering on the polystyrene matrix by exploiting the reactivity of the C−Br bond.

Moreover, because of the well-documented beneficial effect on reactivity of a spacer between the polymer backbone and the tethered substrate, it was decided to incorporate a number of atoms between the cross-linked polystyrene and the fluorinated linker. A generic structure **3** of the so-designed supported proline derivatives is depicted in Figure 1.

Fluoroanisole **2** was first transformed according to the sequence of reactions depicted in Scheme 1. Thus, interaction between **2** and magnesium in diethyl ether led to the corresponding Grignard reagent, which reacted smoothly with allyl bromide to deliver, after purification, the desired propene **5a** in 75% isolated yield.[10] However, no reaction occurred with either 4-bromobut-1-ene (**4b**), 5-bromopent-1-ene (**4c**), or 6-bromohex-1-ene (**4d**), thereby showing the need for an activated bromide in this reaction.[11] A reverse reaction sequence was attempted by preparing the organomagnesium and organozinc derivatives of **4d** and coupling the metalated reactants to **2** under palladium(0) or nickel(0) catalysis. However, only traces of the desired product **5d** were detected under a variety of conditions, and the major

Scheme 1[a]



[a] (i) Mg, Et_2O, 36 °C, 0.5 h. (ii) $H_2C{=}CH{-}(CH_2)_n{-}Br$ ($n = 1$, **4a**; $n = 2$, **4b**; $n = 3$, **4c**; $n = 4$, **4d**), THF, 25 °C, 1.5 h. (iii) $NaBH_4$, $BF_3.Et_2O$, $(CH_3)_2C{=}CH{-}CH_3$, THF, 0−25 °C, 2 h. (iv) H_2O_2, NaOH, H_2O, 1 h. (v) $SOCl_2$, $CHCl_3$, 25−42 °C, 1 h (**9a**); or $P(C_6H_5)_3$, Br_2, CH_3CN, 0 °C, 0.5 h (**9b**); or imidazole, $P(C_6H_5)_3$, I_2, CH_2Cl_2, 0−25 °C, 5 h (**9c**). (vi) $HO{-}(CH_2)_o{-}OH$ ($o = 4$, **10a**; $o = 9$, **10b**), NaH, THF, 56 °C, 6 h.

compounds (when formed) were the reduced, 2-fluoroanisole (**6**) or the 3,3′-difluoro-4,4′-dimethoxybiphenyl (**7**) resulting from the homocoupling process of **2**.

Propene derivative **5a** was then regioselectively converted into alcohol **8** by applying a classical sequence of hydroboration (using di-*sec*-isoamylborane) and oxidation.[12] This alcohol was isolated in excellent yield and constituted the template from which chloride **9a**, bromide **9b**, and iodide **9c** were generated in yields ranging from 83 to 91% using literature procedures.

This approach, thus, delivered our linker flanked by a 3-atom side chain but failed to produce analogous compounds featuring a longer arm. It was, thus, decided to react halogenated derivatives **9** with 1,4-butanediol (**10a**) and 1,9-nonanediol (**10b**) under basic conditions. Interaction of **9a** with 2.5 equiv of **10a** in a 3:1 mixture of tetrahydrofuran (THF) and *N*,*N*-dimethylformamide (DMF) in the presence of sodium hydride at 56 °C led exclusively to the desired substitution product, albeit in low yield (30%). Bromide **9b** afforded a better yield (53%), but inspection of the crude ^1H NMR spectrum indicated the presence of alkene **5a**, resulting from a competitive elimination process. The latter transformation was completely favored in the case of iodide **9c**, with **5a** becoming the exclusive product. Eventually, synthesis of alcohol **11a** was optimized from bromide **9b** in refluxing THF: a 92:8 mixture of **11a**/**5a** was now produced, from which **11a** could reproducibly be isolated in 75% yield. The use of nonanediol **10b** under similar conditions delivered alcohol **11b** (62% isolated yield).

Alcohols **8**, **11a**, and **11b** were then tethered on various chlorinated 1% polystyrenes corresponding to the generic structure **12** (Figure 2). Loadings of 0.8 and 2.5 mmol/g of resin were used in the case of Merrifield polymer **12a** ($q = 1$), whereas polymers **12b**−**e** were synthesized by way of two sequential treatments of 1% cross-linked polystyrene with *n*-butyllithium in refluxing cyclohexane and

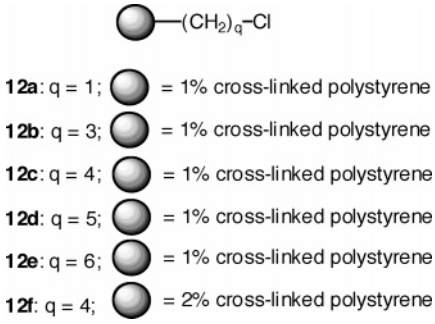


Figure 2. Structures of the various resins **12**.

Table 1. Results from the Manual and Automated Alkylation of Cross-Linked Polystyrene

entry	polymer	% DVB[c]	q	% Br[d]	n_{Br}[e]	% Cl[d]	n_{Cl}[e]	yield (%)[f]
1[a]	**12f**	2	4	0.20	0.025	8.63	2.43	26
2[b]	**12f**	2	4	0.06	0.07	8.47	2.38	25
3[b]	**12b**	1	3	1.06	0.13	7.03	1.98	22
4[b]	**12c**	1	4	0.08	0.01	9.34	2.63	27
5[b]	**12d**	1	5	0.07	0.009	8.96	2.52	26
6[b]	**12e**	1	6	0.08	0.01	8.77	2.47	26

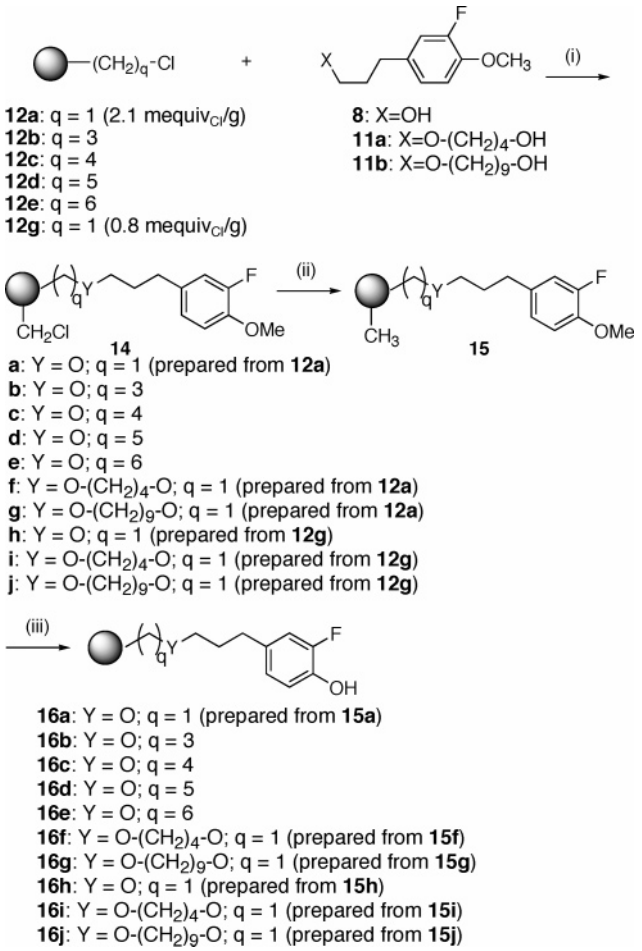
[a] Manual. [b] Automated. [c] % DVB = cross-linking (% of divinylbenzene in the polymer). [d] From elemental analysis. [e] In mequiv per gram of resin. [f] Percent of alkylated cycles on the polymer [$(n_{Cl} + n_B/n_{cycles}) \times 100$].

in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), followed by quenching of the resultant lithiated polymer with 1-bromo-3-chloropropane (**13a**), 1-bromo-3-chlorobutane (**13b**), 1-bromo-5-chloropentane (**13c**), and 1-bromo-6-chlorohexane (**13d**).[13]

We found that these alkylating processes can easily be conducted in an automated way by using a commercially available synthesizer.[14] Thus, for instance, carrying out this reaction with 2% cross-linked polystyrene in a classical round-bottomed flask using gentle magnetic stirring with bromide **13b** delivered, after workup, a polymer **12f**, which was submitted to elemental analysis. Results indicated an 8.63% mass incorporation of chlorine, along with <0.2% mass remnant bromine (Table 1, entry 1). When this transformation was performed in an automated manner, a material characterized by an 8.47% mass incorporation of chlorine and 0.06% mass of bromine was produced (entry 2). Analogously, 1% cross-linked polystyrene and dihaloalkanes **13a**−**d** yielded the corresponding polymers **12b**−**e** with excellent chlorine incorporation (7.03−9.34% mass) (entries 3−6). These data translated into percentages of alkylated phenyl rings ranging from 22 to 27, in accordance with literature data on related reactions.[15] The power and reliability of automation was further confirmed by an experiment similar to that of entry 4; this time, however, the polymer was subjected to a single treatment with *n*-butyllithium. Analysis demonstrated 8.91 and 0.14% mass incorporation of chlorine and bromine, respectively.

Reacting polymers **12a**−**e** with alcohol **8** allowed us to generate new resins featuring both a spacer, comprising 5−10 atoms, and the fluorinated linker. This was achieved by heating a DMF mixture of **8**, the requisite polymer and sodium hydride, along with a catalytic amount of 18-6 crown ether (Scheme 2). Complete consumption of **8** was reached

Scheme 2[a]



[a] (i) NaH, 18−6 crown ether (2% mol), DMF, 80 °C, 15 h (**14a**, **14h**−**j**) or 48 h (**14b**−**g**). (ii) Et_3BHLi, THF, reflux, 15 h. (iii) EtSLi, DMF, 100 °C.

after 15 h (**12a**) or 48 h (**12b**−**e**), and a classical workup delivered resins **14a**−**e**. Elemental analysis indicated the presence of 2.41−2.71% mass of fluorine and 0.53−0.98% mass of unconsumed chlorine, corresponding to yields of 89−70% for the Williamson reaction (Table 2).

Commercially available Merrifield resin (**12a**; n_{Cl} = 2.1 mequiv/g) was also reacted with alcohols **11a** and **11b** under similar conditions to yield polymers **14f** and **14g** (Scheme 2; Table 2, entries 6 and 7). In addition, interactions between Merrifield resin **12g** featuring a low chlorine loading (n_{Cl} = 0.8 mequiv/g) and alcohols **8**, **11a**, and **11b** were also carried out and afforded products **14h**−**j** (Table 3, entries 8−10). The yields in Table 2 clearly indicate that the efficiency of the substitution reaction decreases with the distance from the polymeric matrix or when the size of the nucleophilic species increases. Furthermore, the reaction with resin **12g** (low loading) is the least efficient, furnishing the products in moderate to low yields; no improvement was noted when resins **14g** or **14j** were subjected to a second run of ether formation.

The yields in Table 2 also show that some of the chloromethylene units do not react with the alcoholates under the reaction conditions. To avoid any competitive process in the rest of the synthesis or in the use of the final resins, the unreacted halomethylenes were reduced by interaction

Table 2. Analysis and Yields of Polymers **14a−j**

entry	starting polymer	starting n_{Cl}[a]	q	X	product	% Cl[b]	n_{Cl}[a]	% F[b]	n_F[a]	yield (%)[c]
1	**12a**	2.1	1	O	**14a**	0.53	0.15	2.71	1.42	89
2	**12b**	1.98	3	O	**14b**	0.63	0.18	2.49	1.31	86
3	**12c**	2.63	4	O	**14c**	0.98	0.28	2.60	1.37	72
4	**12d**	2.52	5	O	**14d**	0.68	0.19	2.59	1.37	74
5	**12e**	2.47	6	O	**14e**	0.81	0.23	2.41	1.27	70
6	**12a**	2.1	1	$O-(CH_2)_4-O$	**14f**	0.93	0.26	2.16	1.14	79
7	**12a**	2.1	1	$O-(CH_2)_9-O$	**14g**	1.83	0.51	1.36	0.71	55
8	**12g**	0.8	1	O	**14h**	0.43	0.12	1.05	0.55	78
9	**12g**	0.8	1	$O-(CH_2)_4-O$	**14i**	0.56	0.16	0.90	0.48	70
10	**12g**	0.8	1	$O-(CH_2)_9-O$	**14j**	1.47	0.41	0.36	0.19	29

[a] In mequiv per gram of resin. [b] From elemental analysis. [c] $[n_F/n_{F,max}) \times 100]$ in which $n_{F,max} = n_{F,max}/1 + n_{Cl}$ (MW(alcohol) − MW(HCl)), and MW = molecular weight of the alcohol.

Table 3. Gel-Phase ^{19}F NMR Spectrometry Analysis of Polymer **15d** in Different Solvents

entry	solvent	δ (ppm)[a]	$L_{1/2}$ (ppm)[b]	B (ppm)[c]
1	$CDCl_3$	−136.0	0.24	1.3
2	C_6D_6	−135.0	0.37	1.75
3	toluene-d_8	−135.0	0.40	2.0
4	CD_2Cl_2	−136.8	0.40	1.95
5	THF-d_8	−138.5	0.44	1.95
6	acetone-d_6	−136.5	0.55	1.8
7	CD_3CN	−136.0	1.20	2.9

[a] $CFCl_3$ was used as external reference. [b] Half-height width. [c] Base width.

with lithium triethylborohydride ($LiEt_3BH$).[16] Thus, refluxing a THF mixture of any of polymers **14a−j** and excess $LiEt_3$-BH for 15 h resulted in the clean reduction of all CH_2Cl moieties: elemental analysis of the thereby-formed resins **15a−j** indicated remnant chlorine contents between 0.03 and 0.20% (<0.05 mmol Cl/g).

Resin **15d** was chosen as a model featuring the fluorinated linker and subjected to gel-phase ^{19}F NMR spectrometry analysis by placing 50 mg in an NMR tube, adding the solvent, and waiting 15 min to obtain a homogeneous swollen sample.[17] A study of the optimal solvent was also carried out by recording the spectra of resin **15d** in seven of the most common organic deuterated solvents (Table 3). The results clearly indicate that $CDCl_3$ is the solvent of choice, leading to the best resolved signal, and that more polar solvents induce a lower resolution of the signals (entries 6 and 7). No swelling occurred in deuterated methyl sulfoxide or methanol.

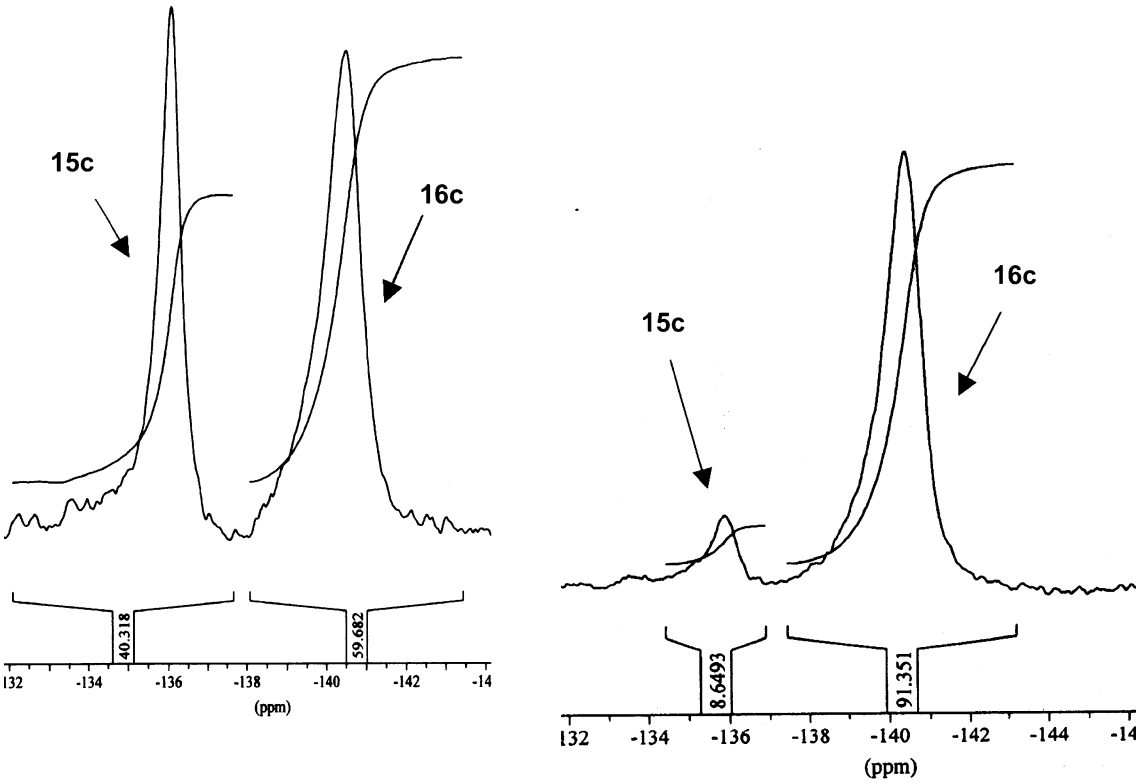
The nine other polymers, **15a−c** and **15e−j**, were subjected to the same treatment, and the ^{19}F NMR spectrometry signals were recorded. Data are gathered in Table 4. The base width of the signals falls between 2.3 and 4.5 ppm with the notable exception of resin **15d** (entry 4). The half-height width, however, differs much more from one resin to another and is not directly related to the length of the spacer. It is noteworthy that the nature of the spacer seems to have a direct influence on the resolution of the signal. Thus, both resins **15e** and **15f** possess a spacer featuring an equal number of atoms (i.e., 10); however, the arm in **15e** contains only one oxygen atom and leads to a better resolved signal. This is somewhat peculiar in view of the known, better resolution of signals in PS−PEG polymers. Finally, comparison between entries 1 (**15a**) and 8 (**15h**), 6 (**15f**) and 9 (**15i**), and 7 (**15g**) and 10 (**15j**) clearly shows that resins featuring low loadings display better resolved ^{19}F NMR signals.

The methoxy unit of the linker was next cleaved selectively by heating at 100 °C a slurry of the requisite resin in DMF in the presence of sodium ethylthiolate.[18] The reaction was monitored by ^{19}F NMR spectrometry in the following manner. A 2.0-mL aliquot of the stirring slurry was taken by syringe, treated briefly with 1 M sulfuric acid, and filtered. Sequential washing of the polymer with anhydrous THF and ether delivered the desired sample. When this simple workup was carried out after 4 h of heating of resin **15c**, the spectra of the resultant sample showed two signals at −136.0 and −140.5 ppm (2:3 ratio) (Figure 3). After 16 h, the ratio had evolved to a 1:9 mixture, and 24 h of heating resulted in the complete disappearance of the signal at −136.0 ppm. The deprotection of all the other resins (**15a−b** and **15d−j**) were conducted and monitored analogously. Thus, the gel-phase ^{19}F NMR spectrometry technique as a means to monitor PS-supported reactions displayed here its full potential. It has to be noted that the method is nondestructive and that the aliquot may be returned to the reaction mixture after having delivered the required information.

Table 4. Gel-Phase ^{19}F NMR Spectrometry Data of Polymers **15a−j** and **16a−j** in $CDCl_3$

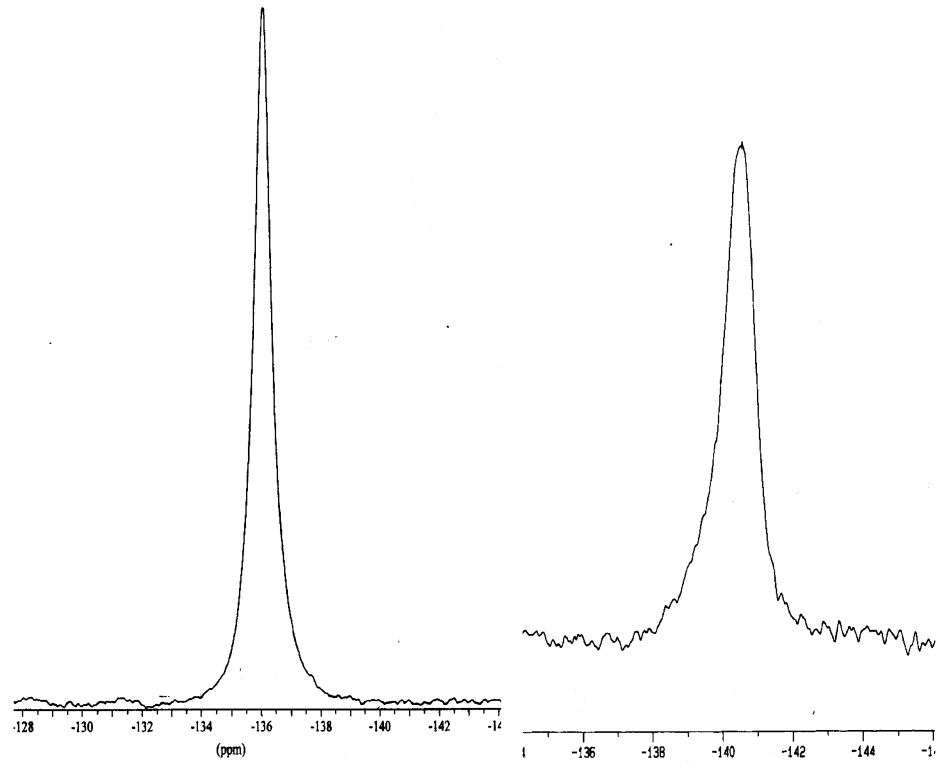
entry	m[a]	resin	δ (ppm)[b]	$L_{1/2}$ (ppm)[c]	B (ppm)[d]	resin	δ (ppm)[b]	$L_{1/2}$ (ppm)[c]	B (ppm)[d]
1	5	**15a**	−135.85	1.00	4.5	**16a**	−139.6	1.60	8.9
2	7	**15b**	−136.00	0.40	3.2	**16b**	−140.6	0.8	3.5
3	8	**15c**	−136.00	0.75	4.2	**16c**	−140.4	1.05	4.2
4	9	**15d**	−136.05	0.35	1.2	**16d**	−140.5	0.80	3.2
5	10	**15e**	−136.10	0.45	3.2	**16e**	−140.4	1.15	4.5
6	10	**15f**	−136.05	0.85	4.0	**16f**	−139.5	2.05	7.1
7	15	**15g**	−135.90	1.35	4.0	**16g**	−141.2	2.30	9.5
8	5	**15h**	−135.90	0.60	3.0	**16h**	−139.4	1.40	4.2
9	10	**15i**	−136.00	0.65	2.3	**16i**	−140.7	1.50	4.7
10	15	**15j**	−136.00	1.06	3.3	**16j**	−139.5	1.95	6.3

[a] Total number of atoms in the spacer. [b] $CFCl_3$ was used as external reference. [c] Half-height width. [d] Base width.



A) 4 h: **15c**/**16c** = 2:3

B) 16 h: **15c**/**16c** = 1:9



C) **15c**: δ = -136.0 ppm

$L_{1/2}$= 0.75 ppm

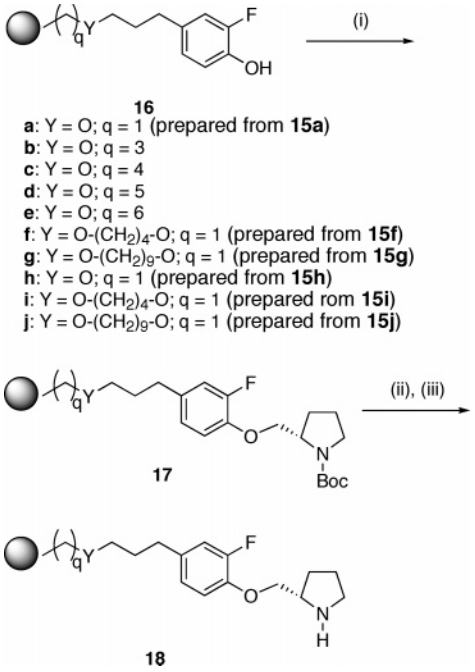
D) **16c**: δ = -140.4 ppm

$L_{1/2}$ = 1.05 ppm

Figure 3. Gel-phase ^{19}F NMR spectra of resin **15c** after 4 h (A) and 16 h (B) and spectra of pure resins **15c** and **16c** (C and D, respectively).

Comparison of the ^{19}F NMR data for both compounds **15c** and **16c** indicates a broadening of the signal in the latter case, the result of a probable intramolecular hydrogen bond (Table 4). Here again, the resins featuring a low loading were

Scheme 3[a]



[a] (i) Ph_3P, DIAD, **1c**, THF, 25 °C. (ii) 10% TFA, CH_2Cl_2, 25 °C, 12 h. (iii) NEt_3, CH_3OH, H_2O, 25 °C.

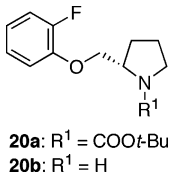


Figure 4. Structures of ethers **20**.

characterized by better resolved signals (compare entries 1 and 8, 6 and 9, and 7 and 10).

With all 10 supported alcohols **16a**−**j** in hand, we turned our attention to their coupling to *N*-Boc-prolinol **1c**. As a model to the supported derivatives **17** (Scheme 3), a Mitsunobu-type reaction was worked out between **1c** and commercially available 2-fluorophenol (**19**).[19] Thus, interaction between **1c** and **19** in the presence of triphenylphosphine (Ph_3P) and diisopropyl azodicarboxylate (DIAD) in THF at 25 °C resulted in the clean formation of ether **20a**, isolated in 79% yield (Figure 4). Removal of the *tert*-butoxycarbonyl group was smoothly achieved under conditions directly transposable to supported substrates and delivered amine **20b** in 93% yield.

The above Mitsunobu reaction conditions were then slightly adapted to solid-phase synthesis by increasing the number of equivalents of Ph_3P, DIAD, and amine **1c** (3 equiv each) and applied to supported alcohol **16a**−**j**, featuring the fluorinated linker (Scheme 3).[20] Here again, monitoring of the reaction was carried out by gel-phase ^{19}F NMR spectrometry, and in the case of alcohols **16a** and **16f**−**j**, completion was observed after 72 h. Alcohols **16b**−**e** underwent conversions ranging from 78 to 91%. Addition of one more equivalent of Ph_3P, DIAD, and **1c** did not induce any further change (24 h at 25 °C or 65 °C).

The chemical shifts of the fluorine nuclei in all 10 ethers **17** were deshielded to −135 ppm (median chemical shifts

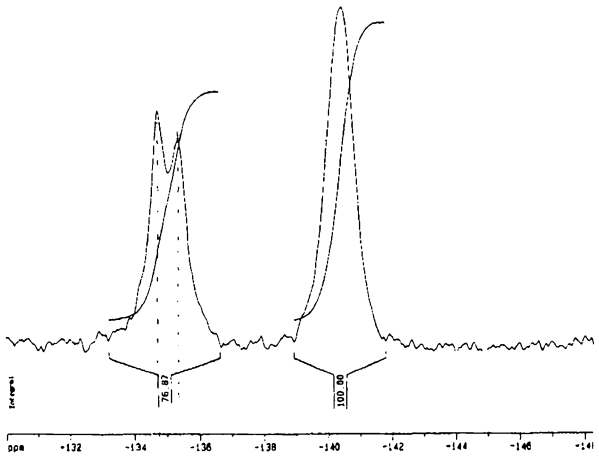


Figure 5. Gel-phase ^{19}F NMR spectrum of an aliquot from the reaction of **16c** and **1c** after 20 h of stirring (43% completion).

of those measured for both rotamers), thus facilitating the monitoring. The two singlets, corresponding to the rotamers of the carbamate group, were separated by ∼0.33 ppm. Figure 5 displays a typical spectrum obtained from the reaction of **16c** recorded after 20 h of reaction (43% completion). *It is of particular interest to note that the fluorine nucleus is able to distinguish between both carbamate rotamers located seven bonds away*. Table 5 contains the pertinent ^{19}F NMR data of ethers **17** (global $L_{1/2}$ and B for both, partly overlapped signals). The measured $L_{1/2}$ and B for each rotamer of **17c** were 0.6 and 1.6 ppm ($\delta = 134.6$ ppm), and 0.7 and 1.23 ppm ($\delta = 135.2$ ppm), respectively. These numbers indicate a sharpening of the signals when compared to those of **16c**.

All polymers **17a**−**j** were subjected to elemental analysis to determine the exact ratio of nitrogen versus fluorine and, thus, cross check the yields obtained from ^{19}F NMR spectrometry. Results compiled in Table 6 indicate that, in most cases, the yields from both techniques match almost perfectly. This validates our approach in a most satisfactory way. The yields thus obtained by ^{19}F NMR spectrometry or from elemental analysis for polymers **17b**−**e** translate into an amount of free, unreacted alcohol functions ranging from 9 to 22% (NMR) or 7 to 24% (elemental analysis) (entries 2−5). Although additional experiments would be needed to ascertain the reasons behind this relative lack of reactivity, one may exclude steric hindrance in view of the result obtained with alcohols **16a** and **16h**.[21] The error was determined to be minimal or to fall within an acceptable range (entries 7 and 10); in the latter cases, competitive processes must intervene and partly destroy the spacer.

The 10 protected amines were then subjected to deprotection by sequentially stirring a CH_2Cl_2 slurry at room temperature for 12 h in the presence of 10 mol % of TFA, and treating with triethylamine in a mixture of methanol/water. Monitoring the reaction by gel-phase ^{19}F NMR spectrometry indicated little change in the chemical shifts; however, the conversion of the two signals of **17** into a single one was accompanied by a sharpening of the peak. The positive incidence of the spacer on this deprotection process is highlighted by the more drastic conditions (50% TFA in CH_2Cl_2, reflux) needed to cleave the *tert*-butoxycarbonyl

Table 5. Gel-Phase ^{19}F NMR Spectrometry Data of Polymers **17a**−**j** and **18a**−**j** in $CDCl_3$

entry	m^a	resin	δ (ppm)^{b,c}	$L_{1/2}$ (ppm)^d	B (ppm)^e	resin	δ (ppm)^b	$L_{1/2}$ (ppm)^d	B (ppm)^e
1	5	**17a**	−134.85	2.25	6.9	**18a**	−134.9	1.60	6.3
2	7	**17b**	−135.1	1.30	3.7	**18b**	−135.0	0.85	3.5
3	8	**17c**	−134.9	1.30	4.2	**18c**	−134.8	0.90	4.2
4	9	**17d**	−135.0	1.30	4.5	**18d**	−134.8	1.10	3.8
5	10	**17e**	−135.1	1.40	3.9	**18e**	−135.0	1.05	4.3
6	10	**17f**	−135.2	2.05	5.9	**18f**	−135.0	1.25	6.5
7	15	**17g**	−135.3	2.15	6.3	**18g**	−135.3	2.85	6.9
8	5	**17h**	−135.15	1.65	5.9	**18h**	−135.1	1.50	7.1
9	10	**17i**	−134.8	1.65	6.0	**18i**	−134.8	2.25	6.8
10	15	**17j**	−135.05	1.95	6.1	**18j**	−135.0	3.05	8.0

[a] Total number of atoms in the spacer. [b] $CFCl_3$ was used as external reference. [c] Median chemical shifts of those measured for both rotamers. [d] Global half-height width for both signals. [e] Global base width for both signals.

Table 6. Fluorine and Nitrogen Content of Resins **17a**−**j** and Comparison of the Yields Obtained from Elemental Analysis and from Gel-Phase ^{19}F NMR Spectrometry

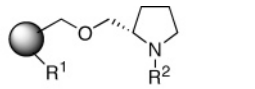
entry	m^a	resin	% F	n^F	% N	n^N	n^{OH} [b]	anal. yield (%)[c]	^{19}F NMR yield (%)	ν (yields) (%)[e]
1	5	**17a**	2.15	1.13	1.54	1.12	−	99	100	1
2	7	**17b**	1.86	0.98	1.16	0.83	0.15	85	88	3
3	8	**17c**	2.20	1.16	1.51	1.08	0.08	93	91	2
4	9	**17d**	2.00	1.05	1.12	0.80	0.25	76	78	2
5	10	**17e**	1.96	1.03	1.30	0.93	0.10	90	90	0
6	10	**17f**	1.43	1.02	1.39	0.99	−	97	100	3
7	15	**17g**	1.05	0.55	0.88	0.63	−	87	100[c]	13
8	5	**17h**	0.99	0.52	0.73	0.52	−	100	100	0
9	10	**17i**	0.74	0.39	0.56	0.40	−	97	100	3
10	15	**17j**	0.29	0.15	0.18	0.13	−	87	100[d]	14

[a] Total number of atoms in the spacer. [b] $n^{OH} = n^F - n^N$. [c] Calculated from the ratio n^N/n^F. [d] Complete consumption of the starting alcohol. [e] $\text{Yield}_{NMR} - \text{yield}_{analysis}$.

Table 7. Fluorine and Nitrogen Content of Resins **18a**−**j**

entry	m^a	resin	% F	n^F	% N	n^N
1	5	**18a**	2.24	1.18	1.68	1.20
2	7	**18b**	1.96	1.13	1.22	0.87
3	8	**18c**	2.38	1.25	1.62	1.16
4	9	**18d**	2.05	1.08	1.24	0.89
5	10	**18e**	2.26	1.19	1.48	1.06
6	10	**18f**	2.33	1.22	1.58	1.13
7	15	**18g**	0.73	0.38	1.06	0.71
8	5	**18h**	1.06	0.56	0.76	0.54
9	10	**18i**	0.86	0.45	0.57	0.41
10	15	**18j**	0.32	0.17	0.07	0.05

[a] Total number of atoms in the spacer.



21a: $R^1 = CH_2Cl$, $R^2 = COOt\text{-Bu}$
21b: $R^1 = CH_3$, $R^2 = COOt\text{-Bu}$
21c: $R^1 = CH_3$, $R^2 = H$

Figure 6. Structures of ethers **21**.

groups of resin **21b**, obtained by a sequential Williamson synthesis involving Merrifield resin (**12a**, 2.1 mequiv Cl/g) and alcohol **1c**, and reduction of the residual chlorine atoms in the thereby-formed **21a** (Figure 6).[22] IR spectrometry allowed here a qualitative monitoring of the reaction (disappearance of the C═O absorption at 1700 cm^{-1}). A classical workup delivered the supported amines, which were subjected to elemental analysis for the determination of the fluorine and nitrogen contents. The results in Table 7 indicate that resins **17a**−**f** and **17h** and **i** underwent a clean reaction (entries 1−6 and 8 and 9, respectively). The discrepancies observed between n^F and n^N in the cases of amines **18b** and **18d** are a reflection of the yields obtained for the Mitsunobu couplings (see above) and not of the deprotection process.[23] Finally, the notable differences observed for amines **18g** and **18j** show that this particular spacer renders the aryl alkyl ether group sensitive to the deprotection conditions (entries 7 and 10). Use of compounds **18a**−**f** and **18h** and **i** in various organochemical reactions is currenly under investigation and will be reported in due course.

Conclusion

Ten cross-linked polystyrene-supported, protected chiral amines featuring both a spacer, comprising from 5 to 15 atoms, and a fluorinated linker have been successfully prepared. The development of the monitoring technique by gel-phase ^{19}F NMR spectrometry on cross-linked polystyrene derivatives proved to be of high value in four steps of the process, as shown by the comparison of data gathered from both a classic NMR spectrometer and elemental analysis. The signals obtained for the fluorine nuclei were found to feature half-height and base widths varying with both the length and the nature of the spacer and exploitable in the context of monitoring when the ^{19}F chemical shifts differ by values between 0.5 and 1.0 ppm, depending on the half-height width. On the basis of the ^{19}F NMR spectrometry measurements, the optimal spacer length (*m* value in **3**) seems to be of 7−10 atoms, depending on the polymer. In that context, it is of note that the two rotamers of carbamates **17** are detected by gel-phase ^{19}F NMR, even though the fluorine nucleus is seven bonds away. Gel-phase ^{19}F NMR spectrometry thus constitutes a useful technique that complements

IR and ^{13}C NMR spectrometries for the qualitative monitoring of reactions. In addition, quantitative determination of the conversion in a given transformation is possible, provided that ^{19}F chemical shifts of the substrate and the product be different enough ($\Delta\delta$ > base width), as illustrated by the Mitsunobu coupling process (**16** → **17**). The technique is nondestructive, and the samples used to monitor the reactions may be returned to the reaction medium. Deprotection of the above amines was achieved and furnished eight of the final resins in good to acceptable purity for future applications. Use of these polymers in asymmetric synthesis is currently under study.[24]

Experimental Section

Cross-linked polystyrene PS-1% DVB and Merrifield resin MR-1%DVB were purchased from commercial sources. Before use, polymers were dried for a couple of hours in a warming desiccator (40 °C/20 mbar). Gel-phase NMR samples were prepared as follows: 50 mg of dry resin was placed in an NMR tube, and deuterated chloroform was slowly added through a 20-cm-long needle plunging down to the bottom of the tube. After swelling of the resin, sonication was used to remove air bubbles within the gel. Unless otherwise indicated, NMR spectra were recorded in deuterated chloroform on spectrometers operating at 200 MHz for proton (^1H), 75 MHz for carbon (^{13}C), and 282 MHz for fluorine (^{19}F). Chemical shifts (δ) are expressed in parts per million (ppm) relative to $(CH_3)_4Si$, $CDCl_3$, and hexafluorobenzene, respectively, and coupling constants (J) are reported in Hertz (Hz). Infrared spectra were recorded on a FT-IR spectrometer; IR spectra of solids and polymers were recorded as KBr pellets and liquids as films (NaCl); wavelenghs (ν) are expressed in cm^{-1}. Low- and high-resolution mass spectra were recorded at the University of Rouen Mass Spectrometry Department.

3-(3-Fluoro-4-methoxyphenyl)prop-1-ene (5a). To a suspension of magnesium (7.30 g, 0.30 mol) in anhydrous ether (100 mL) are added, under nitrogen and at room temperature, 4-bromo-2-fluoromethoxybenzene **(2)** (51.25 g, 0.25 mol) and 1,2-dibromoethane (one drop, catalytic amount) (caution: exothermic reaction). After 30 min, the mixture is cooled to room temperature, and a solution of freshly distilled allyl bromide (**4a**) (26 mL, 0.30 mol) in anhydrous THF (50 mL) is added dropwise over 1.5 h. The resultant reaction mixture is cooled to 0 °C and quenched with an aqueous, saturated solution of NH_4Cl (50 mL). The organic layer is separated, washed twice with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product (yellow oil, 40 g) is purified by distillation under vacuum (Kugelrohr, 100 °C/0.4 mbar) to give product **5a** as a colorless oil (31 g, 75%). ^1H NMR δ 6.93−6.85 (m, 3H), 5.90 (ddt, 1H, $^3J_{trans} = 17.5$, $^3J_{cis} = 9.5$, $^3J = 6.6$), 5.05 (dt, 1H, $^3J_{cis} = 9.3$, $^4J = 1.1$), 5.04 (dt, 1H, $^3J_{trans} = 17.5$, $^4J = 1.5$), 3.85 (s, 3H), 3.29 (d, 2H, $^3J = 6.6$). ^{19}F NMR (188 MHz) δ −136.0 (m, 1F). ^{13}C NMR δ 152.7 (d, $^1J_{C-F} = 244.3$), 146.3 (d, $^2J_{C-F} = 11.2$), 137.5, 133.5 (d, $^3J_{C-F} = 5.6$), 124.4 (d, $^3J_{C-F} = 3.5$), 116.7 (d, $^2J_{C-F} = 17.6$), 116.5, 113.8, 56.7, 39.9. MS (EI) *m/z* (rel. int.) 166 ($M^{+\bullet}$, 100), 151 (34), 135 (37), 103 (30), 77 (48). IR (NaCl) ν 1520, 1285, 1225, 1130, 1030. Anal. Calcd for $C_{10}H_{11}FO$: C, 72.27; H, 6.67. Found: C, 72.15; H, 6.56.

Attempted Coupling Reaction between Bromide 2 and 5-Hexenylzinc Chloride. 3,3′-Difluoro-4,4′-dimethoxybiphenyl (7). A solution of 5-hexenylzinc chloride (1.2 mmol, 1.2 equiv) in a mixture of THF/Et_2O (2 mL:1.5 mL) is prepared as follows. To magnesium (36 mg, 1.5 mmol) and 6-bromohex-1-ene (0.16 mL, 1.2 mmol, 1.2 equiv) in anhydrous THF (2 mL) at room temperature is added a catalytic amount of 1,2-dibromoethane. The mixture is stirred for 1 h, after which a freshly prepared 1 M solution of zinc chloride (1.5 mL, 1.5 mmol) in ether is added dropwise. Stirring is continued for 1.5 h, and the resultant slurry is added dropwise to a solution of tetrakis(triphenylphosphine)-palladium (60 mg, 0.05 mmol, 0.05 equiv) and bromide **2** (205 mg, 1 mmol) in anhydrous THF (2 mL). The mixture is refluxed for 16 h, cooled, and filtered through silica, which is then rinsed with Et_2O (2 × 20 mL). The combined organic layers are washed with 1 M aqueous HCl (2 × 20 mL) and 1 M aqueous $NaHCO_3$ (20 mL). Drying over magnesium sulfate, filtration, and evaporation of the volatile leaves a crude sample, which is chromatographed on silica. Elution with pentane/Et_2O yields compound **7** as a colorless solid (81 mg, 65%). mp 152−154 °C (lit: 153.5 °C). ^1H NMR δ 7.28−7.18 (m, 4H), 7.03−6.94 (m, 2H), 3.90 (s, 6H). ^{19}F NMR (188 MHz) δ 27.4−27.3 (m, 2F). MS (EI) *m/z* (rel. int.) 250 ($M^{+\bullet}$, 80), 235 (100), 220 (8), 207 (20), 192 (22), 164 (14), 125 (7).[25]

3-(3-Fluoro-4-methoxyphenyl)propan-1-ol (8). To a suspension of $NaBH_4$ (3.80 g, 0.10 mol) in anhydrous THF (250 mL) cooled to 0 °C is introduced freshly distilled 2-methylbut-2-ene (28 mL, 0.27 mol). A solution of $BF_3 \cdot Et_2O$ (17 mL, 0.13 mol) is next added dropwise while keeping the temperature below 10 °C. The mixture is stirred for 10 min and cooled to 0 °C, and a solution of **5a** (16.60 g, 0.10 mol) in anhydrous THF (50 mL) is added dropwise over 1 h. The reaction mixture is allowed warm to room temperature (∼1 h). ^1H NMR monitoring revealed the complete disappearance of the ethenyl hydrogens. The reaction mixture is cooled to 0 °C and quenched with MeOH (10 mL). A 3 M aqueous solution of NaOH (44 mL, 0.13 mol) is added dropwise while keeping the reaction temperature below 30 °C. The mixture is then oxidized by adding drop-by-drop a solution of 30% hydrogen peroxyde in water (45 mL, 0.40 mol) while keeping the temperature under 50 °C. The solution is stirred at the same temperature for 1 h. Removal of THF and addition of ether (250 mL) to the residue leads to a bilayer system, which was separated. The aqueous layer is extracted with ether (200 mL). The combined organic phases are washed twice with a saturated solution of NH_4Cl (2 × 50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Volatiles are eliminated by distillation under vacuum (Kugelrohr, 50 °C/0.5 mbar), and pure **8** is isolated as a colorless liquid (16.90 g, 92%). ^1H NMR δ 6.91−6.77 (m, 3H), 3.82 (s, 3H), 3.60 (t, 2H, $^3J = 8.3$), 2.59 (t, 2H, $^3J = 4.0$), 2.16 (br s, 1H), 1.80 (qt, 2H, $^3J = 6.6$). ^{19}F NMR (188 MHz) δ −136.1 (m, 1F). ^{13}C NMR δ 152.6 (d, $^1J_{C-F} = 243.6$), 146.0 (d, $^2J_{C-F} = 11.2$), 135.4 (d, $^3J_{C-F} = 6.3$), 124.3 (d, $^3J_{C-F} = 3.5$), 116.4 (d, $^2J_{C-F} =$

17.6), 113.8 (d, $^4J_{C-F}$ = 2.1), 62.2, 56.7, 34.4, 31.4. MS (EI) *m*/*z* (rel. int.) 184 ($M^{+\bullet}$, 43), 166 (17), 139 (100), 109 (15), 96 (14), 77 (29). Anal. Calcd for $C_{10}H_{13}FO_2$: C, 65.20; H, 7.11. Found: C, 65.09; H, 7.16.

4-(3-Chloropropyl)-2-fluoromethoxybenzene (9a). To a solution of alcohol **8** (1.40 g, 7.60 mmol) in chloroform (10 mL) under nitrogen is added dropwise thionyl chloride (1.1 mL, 15.2 mmol, 2.0 equiv). The mixture is then refluxed for 30 min, cooled to room temperature, and evaporated. The crude residue is purified by Kugelrohr distillation (140 °C/0.2 mmHg) to yield pure chloride **9a** in the form of a colorless liquid (1.25 g, 83%). ^{1}H NMR δ 6.93−6.85 (m, 3H), 3.85 (s, 3H), 3.49 (t, 2H, ^3J = 6.6), 2.69 (t, 2H, ^3J = 7.3), 2.02 (qt, 2H, ^3J = 6.6). ^{19}F NMR (188 MHz) δ −135.88 (m, 1F). ^{13}C NMR δ 152.7 (d, $^1J_{C-F}$ = 245.6), 146.3 (d, $^2J_{C-F}$ = 10.2), 134.1 (d, $^3J_{C-F}$ = 5.8), 124.5 (d, $^3J_{C-F}$ = 2.9), 116.5 (d, $^2J_{C-F}$ = 18.2), 113.9 (d, $^4J_{C-F}$ = 2.2), 56.7, 44.1, 34.3, 32.1. MS (EI) *m*/*z* (rel. int.) 204 ($M^{+\bullet}$, ^{37}Cl, 20), 202 ($M^{+\bullet}$, ^{35}Cl, 6), 139 (100), 109 (8), 96 (11), 77 (12). IR (NaCl) ν 1518, 1274, 1224, 1122, 1028. Exact mass calcd for $C_{10}H_{12}ClFO$: 202.0561 (^{35}Cl), 204.0533 (^{37}Cl). Found: 202.0565 (^{35}Cl), 204.0502 (^{37}Cl).

4-(3-Bromopropyl)-2-fluoromethoxybenzene (9b). Bromine (2 mL, 40 mmol) is added dropwise under nitrogen to a solution of PPh_3 (10.5 g, 40 mmol) in anhydrous acetonitrile (50 mL) at 0 °C. A white precipitate forms, and the solution turns slightly yellow. Alcohol **8** (7.4 g, 40 mmol) is then added while keeping the reaction temperature below 10 °C. Evaporation of acetonitrile, addition of *n*-pentane (50 mL), filtration over silica, and concentration of the filtrate under reduced pressure yields bromide derivative **9b** (colorless liquid, 9.0 g, 91%). ^{1}H NMR δ 6.93−6.85 (m, 3H), 3.85 (s, 3H), 3.35 (t, 2H, ^3J = 6.6), 2.69 (t, 2H, ^3J = 7.3), 2.10 (qt, 2H, ^3J = 6.9). ^{19}F NMR (188 MHz) δ −135.8 (m, 1F). ^{13}C NMR δ 152.7 (d, $^1J_{C-F}$ = 245.6), 146.3 (d, $^2J_{C-F}$ = 10.9), 134.0 (d, $^3J_{C-F}$ = 5.8), 124.5 (d, $^3J_{C-F}$ = 3.6), 116.6 (d, $^2J_{C-F}$ = 18.2), 113.9 (d, $^4J_{C-F}$ = 2.2), 56.8, 34.4, 33.3, 33.2. MS (EI) *m*/*z* (rel. int.) 248 ($M^{+\bullet}$, ^{81}Br, 26), 246 ($M^{+\bullet}$, ^{79}Br, 27), 139 (100), 109 (5), 96 (8), 77 (7). IR (NaCl) ν 1518, 1272, 1224, 1118, 1028. Exact mass (CI, 200 eV) *m*/*z* calcd for $C_{10}H_{12}BrFO$: 246.0056 (^{79}Br), 248.0036 (^{81}Br). Found: 246.0028 (^{79}Br), 248.0010 (^{81}Br).

4-(3-Iodopropyl)-2-fluoromethoxybenzene (9c). To a cold (0 °C) mixture of triphenylphosphine (2.9 g, 11 mmol, 1.1 equiv) and imidazole (2.0 g, 30 mmol, 3 equiv) in methylene chloride (50 mL) is added in one addition iodine (2.8 g, 11 mmol, 1.1 equiv). After 2 min of stirring, a solution of alcohol **8** (1.8 g, 10 mmol) in methylene chloride (25 mL) is added in such a way as to keep the internal flask temperature below 10 °C. Stirring is continued at room temperature in the dark for 4 h. Excess iodine is then destroyed by way of a saturated solution of sodium sulfite (20 mL). The organic layer is then washed twice with 0.01 M aqueous HCl (2 × 20 mL) and dried over magnesium sulfate. Evaporation of the volatiles under reduced pressure, addition of *n*-pentane to the residue, and filtration of the solution over silica led after concentration under vacuum to colorless, liquid iodide **9c** (2.4 g, 83% yield). ^{1}H NMR δ 6.93−6.85 (m, 3H), 3.85 (s, 3H), 3.13 (t, 2H, ^3J = 6.6), 2.64 (t, 2H, ^3J = 7.3), 2.06 (qt, 2H, ^3J = 6.9). ^{19}F NMR (188 MHz) δ −135.8 (m, 1F). ^{13}C NMR δ 152.7 (d, $^1J_{C-F}$ = 244.1), 146.3 (d, $^2J_{C-F}$ = 10.2), 133.9 (d, $^3J_{C-F}$ = 5.8), 124.5 (d, $^3J_{C-F}$ = 3.6), 116.6 (d, $^2J_{C-F}$ = 18.2), 113.9 (d, $^4J_{C-F}$ = 2.2), 56.7, 35.6 (d, $^4J_{C-F}$ = 1.5), 35.1, 6.47. MS (EI) *m*/*z* (int. rel.) 294 ($M^{+\bullet}$, 27), 139 (100), 96 (16), 77 (19). IR (NaCl) ν 1525, 1280, 1225, 1125, 1025.

4-[3-(3-Fluoro-4-methoxyphenyl)propoxy]butan-1-ol (11a) and 9-[3-(3-Fluoro-4-methoxyphenyl)propoxy]nonan-1-ol (11b). General Procedure. To a suspension of NaH (1.0 equiv) in anhydrous THF (2 mL/mmol of NaH), cooled to 0 °C, are added sequentially, under nitrogen, (18-6) crown ether (1% mol equiv) and a concentrated solution of the desired diol **10** (2.5 equiv) in THF (0.3 mL/mmol of diol **10**). The stirring mixture is warmed to room temperature, and after 10 min, a solution of bromide **9b** (1.0 equiv) in anhydrous THF (1 mL/mmol of **9b**) is added dropwise. The resultant solution is refluxed for 6 h and cooled to 0 °C. Addition of MeOH (1 mL/mmol of NaH) and concentration under reduced pressure leaves to a residue to which is added ether (2 mL/mmol of diol **10**). The organic layer is washed twice with water and twice with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product is purified by flash chromatography on silica and eluted with *n*-pentane/ether (8:2) first, then with ether to afford the desired alcohol (**11a**, 75%, colorless oil; **11b**, 62%, colorless oil). **11a**: ^{1}H NMR δ 6.91−6.83 (m, 3H), 3.83 (s, 1H), 3.63 (m, 2H), 3.42−3.40 (m, 4H), 2.59 (t, 2H, ^3J = 7.5), 1.82 (q, 2H, ^3J = 7.0), 1.66 (m, 4H). ^{19}F NMR (188 MHz) δ −136.3 (m, 1F). ^{13}C NMR δ 152.7 (d, $^1J_{C-F}$ = 243.5), 146.5 (d, $^2J_{C-F}$ = 10.7), 135.4 (d, $^3J_{C-F}$ = 5.9), 124.3 (d, $^3J_{C-F}$ = 3.4), 116.5 (d, $^2J_{C-F}$ = 17.8), 113.8 (d, $^4J_{C-F}$ = 2.1), 71.3, 70.3, 63.2, 56.8, 31.7, 31.5, 30.8, 27.3. MS (EI) *m*/*z* (rel. int.) 256 ($M^{+\bullet}$, 8), 184 (17), 166 (100), 151 (14), 139 (34). IR (NaCl) ν 3390, 1518, 1274, 1126. Exact mass calcd for $C_{14}H_{21}FO_3$: 256.1475. Found: 256.1484. **11b**: ^{1}H NMR δ 6.91-6.83 (m, 3H), 3.83 (s, 3H), 3.60 (t, 2H, ^3J = 6.4), 3.36 (t, 4H, ^3J = 6.4), 2.59 (t, 2H, ^3J = 7.7), 1.81 (q, 2H, ^3J = 7.0), 1.53−1.28 (m, 14H). ^{19}F NMR (188 MHz) δ −136.3 (m, 1F). ^{13}C NMR δ 152.6 (d, $^1J_{C-F}$ = 243.2), 146.0 (d, $^2J_{C-F}$ = 10.2), 135.6 (d, $^3J_{C-F}$ = 5.8), 124.3 (d, $^3J_{C-F}$ = 2.9), 116.5 (d, $^2J_{C-F}$ = 17.4), 113.8 (d, $^4J_{C-F}$ = 2.2), 71.4, 70.0, 63.4, 56.8, 31.8, 31.6, 30.1, 29.9, 29.8, 29.8, 29.7, 26.6, 26.1. MS (EI) *m*/*z* (rel. int.) 326 ($M^{+\bullet}$, 13), 166 (100), 151 (6), 139 (18). IR (NaCl) ν 3370, 1518, 1273, 1126. Exact mass calcd for $C_{19}H_{31}FO_3$: 326.2257. Found: 326.2237.

Poly-*meta*,*para*-lithium Polystyrene. Dried PS-1% DVB or PS-1% DVB (2.1 g, 20 mmol of aromatic rings) is introduced in a Schlenk tube under argon. Anhydrous cyclohexane (15 mL) and freshly distilled TMEDA (3 mL, 20 mmol) are added at room temperature, and the resultant mixture is stirred for a few minutes to obtain a homogeneously swollen resin. A 2.5 M solution of *n*-BuLi in hexane (10 mL, 25 mmol) is then added dropwise, and the mixture is refluxed for 6 h. Heating is discontinued, and after cooling, the liquid is transferred under argon pressure, via a cannula, into a flask containing 2-propanol (20 mL). Then anhydrous cyclohexane (15 mL) is added on the resin, and stirring is resumed for 5 min, after which the liquid is transferred onto

2-propanol, via a cannula, under argon pressure. This rinsing operation is repeated twice more. A second *n*-BuLi treatment, identical to the one described above, is carried out, the slurry is cooled to room temperature, stirring is discontinued, and the liquid is transferred to an excess of 2-propanol. The lithiated polymer is rinsed six times by addition of anhydrous cyclohexane (6 × 15 mL), followed by removal of the solvent by way of an argon pressure. The thereby obtained orange resin is then alkylated with 1-bromo-*m*-chloroalkanes **13a**−**d** (m = 3, 4, 5, 6).

Poly-*meta,para*-chloroalkylpolystyrenes (Alkyl = *n*-Propyl, *n*-Butyl, *n*-Pentyl, *n*-Hexyl) (12b−**f). General Procedure.** The lithiated polymer obtained above (20 mmol of aromatic rings partially lithiated) is swollen by stirring in anhydrous THF (15 mL) under argon for 5 min. The stirring slurry is then cooled to 0 °C, and the requisite 1-bromo-*m*-chloroalkane **13a**−**d** (m = 3, 4, 5, 6) (20 mmol) is added dropwise, leading to instantaneous resin bleaching. The mixture is stirred 4 h at room temperature, and the polymer is filtered, sequentially washed with a 1:1 mixture of H_2O/MeOH (20 mL) and THF (3 × 20 mL), and dried in a warming desiccator under reduced pressure (40 °C/20 mbar). **12b**−**f**: IR ν (cm^{-1}) 1250. Factor of alkylated rings: $T_{Ana} = [(n^{Cl} + n^{Br})/n^{rings}]$.[26] **12b**: Anal. found: Br, 1.06 (n^{Br} = 0.13); Cl, 7.03 (n^{Cl} = 2.00). T_{Ana} = 22%.[27] **12c**: Anal. found: Br, 0.08 (n^{Br} = 0.01); Cl, 9.34 (n^{Cl} = 2.60). T_{Ana} = 27%. **12d**: Anal. found: Br, 0.07 (n^{Br} < 0.01); Cl, 8.96 (n^{Cl} = 2.5). T_{Ana} = 26%. **12e**: Anal. found: Br, 0.08 (n^{Br} = 0.01); Cl, 8.77 (n^{Cl} = 2.5). T_{Ana} = 26%. **12f**: Anal. found: Br, 0.06 (n^{Br} < 0.01); Cl, 8.47 (n^{Cl} = 2.4). T_{Ana} = 25%.

Introduction of the Fluorinated Linkers on Solid Supports. General Procedure. In a Schlenk tube are successively introduced the requisite polymer, either commercially available MR-1% DVB **12a** (n^{Cl} = 2.1) or MR-1% DVB **12g** (0.8 mmol/g), or one of the synthesized polymers **12b**−**e** (n^{Cl} = 2.0−2.6 mmol/g), NaH (1.1−1.3 equiv), and a catalytic amount of 18-crown-6 (2−3% mol). Anhydrous DMF (8−10 mL/g of resin) is added to the Schlenk tube, under nitrogen. The slurry is stirred for a few minutes at room temperature to allow the resin to swell, and a solution of the requisite alcohol **8**, **11a,** or **11b** (1.1−1.3 equiv) in DMF is carefully added. The mixture is warmed to 80 °C for 15 h (**12a** and **12g**) or for 48 h (**12b**−**e**). The slurry is cooled to room temperature and hydrolyzed with a 1:1 mixture of H_2O/MeOH (4−5 mL/g of polymer). After filtration, the resin is sequentially rinsed with EtOH, THF, and ether (15−20 mL of each solvent/g of polymer). The polymer thus obtained is dried in a warming desiccator under reduced pressure (40 °C/20 mbar) and characterized by the alcohol incorporation factor, T_{Ana}.

Poly-*meta,para*-[3-(3-fluoro-4-methoxyphenyl)propoxy]-alkyl-poly-*meta,para*-chloroalkylpolystyrenes (14b−**e) (Alkyl = *n*-Propyl, *n*-Butyl, *n*-Pentyl, *n*-Hexyl; *o* = 3, 4, 5, 6, Respectively).** IR ν 1250. **14b** (o = 3, m = 7): T_{Ana} = 86%. Anal. found: Cl, 0.63; F, 2.49 (n^F = 1.31). ^{19}F NMR δ −136.0, $L_{1/2}$ = 0.40.[28] **14c** (o = 4, m = 8): T_{Ana} = 72%. Anal. found: Cl, 0.98; F, 2.60 (n^F = 1.37). ^{19}F NMR δ −136.1, $L_{1/2}$ = 0.75. **14d** (o = 5, m = 9): T_{Ana} = 74%. Anal. found: Cl, 0.68; F, 2.59 (n^F = 1.37). ^{19}F NMR δ −136.1, $L_{1/2}$ = 0.25. **14e** (o = 6, m = 10): T_{Ana} = 70%. Anal. found: Cl, 0.81; F, 2.41 (n^F = 1.27). ^{19}F NMR δ −136.1, $L_{1/2}$ = 0.45.

Poly-*para*-[3-(3-fluoro-4-methoxyphenyl)propoxy]-alkoxymethyl-poly-*para*-chloromethylpolystyrenes (14f, 14i, Alkoxy = Butoxy and 14g, 14j, Alkoxy = Nonoxy). IR ν 1250. **14f** (m = 10): T_{Ana} = 79%. Anal. found: Cl, 0.93; F, 2.16 (n^F = 1.14). ^{19}F NMR δ −136.1, $L_{1/2}$ = 0.85. **14i** (m = 10): T_{Ana} = 70%. Anal. found: Cl, 0.56; F, 0.90 (n^F = 0.48). ^{19}F NMR δ −136.0, $L_{1/2}$ = 0.65. **14g** (m = 15): T_{Ana} = 55%. Anal. found: Cl, 1.83; F, 1.36 (n^F = 0.71). ^{19}F NMR δ −136.0, $L_{1/2}$ = 1.25. **14j** (m = 15): T_{Ana} = 29%. Anal. found: Cl, 1.47; F, 0.36 (n^F = 0.19). ^{19}F NMR δ −136.0, $L_{1/2}$ = 1.05.

Poly-*para*-[3-(3-fluoro-4-methoxyphenyl)propoxymethyl]-poly-*para*-chloromethylpolystyrenes (14a, 14h). IR ν 1250. **14a** (m = 5): T_{Ana} = 89%. Anal. found: Cl, 0.53; F, 2.71 (n^F = 1.42). ^{19}F NMR δ −136.0, $L_{1/2}$ = 0.75. **14h** (m = 5): T_{Ana} = 78%. Anal. found: Cl, 0.43; F, 1.05 (n^F = 0.55). ^{19}F NMR δ −135.9, $L_{1/2}$ = 0.60.

Poly-*para*-(*N*-*tert*-butoxycarbonylpyrrolidin-2(*S*)-yl-methoxymethyl)poly-*para*-chloropolystyrene (21a). Resin **12a** (2.1 mequiv/g, 1% DVB), NaH (1.0 equiv), *N*-BOC prolinol **1c** (1 equiv) and 18-crown-6 (5% mol equiv) are placed in a Schlenck reactor. Under nitrogen, anhydrous DMF (8−10 mL/g of **12a**) is added at room temperature and gently stirred for 6 h at 80 °C. At room temperature, a 1:1 mixture of H_2O/MeOH (4−5 mL/g of **12a**) is added and the mixture is stirred an additional 1 h, after the polymer is filtered, sequentially washed successively with EtOH, anhydrous THF, and anhydrous ether (10−15 mL/g of **12a**) and dried in a warming desiccator under reduced pressure (40 °C/20 mbar). **21a**: IR ν (cm^{-1}) 1700, 1250. Anal. found: N, 1.94 (n^N = 1.39); Cl, 1.22 (n^{Cl} = 0.34). T_{Ana} = 89%.

Reduction of Residual Chloromethylene Groups. General Procedure. The requisite resin (**14a**−**j** and **21a**) is placed in a Schlenck tube under nitrogen and swollen in anhydrous THF (10 mL/g of polymer). A 1 M THF solution of $LiEt_3BH$ (0.8−1.0 mL/g of polymer) is slowly added at room temperature, and the mixture is refluxed overnight. Hydrolysis is carried out at room temperature by adding a 1:1 mixture of H_2O/MeOH. The resin is filtered and sequentially rinsed with THF and ether (15−20 mL/g of polymer). The polymer is then dried in a warming desiccator under reduced pressure (40 °C/20 mbar).

Poly-*meta,para*-[3-(3-fluoro-4-methoxyphenyl)propoxy]-alkylpolystyrenes (15b−**e) (Alkyl = *n*-Propyl, *n*-Butyl, *n*-Pentyl or *n*-Hexyl, *o* = 3, 4, 5 or 6, Respectively). 15b** (o = 3, m = 7): Anal. found: Cl, 0.09 (n^{Cl} < 0.03). ^{19}F NMR δ −136.0, $L_{1/2}$ = 0.40. **15c** (o = 4, m = 8): Anal. found: Cl, 0.07 (n^{Cl} = 0.02). ^{19}F NMR δ −136.0, $L_{1/2}$ = 0.75. **15d** (o = 5, m = 9): Anal. found: Cl, 0.14 (n^{Cl} < 0.04). ^{19}F NMR δ −136.1, $L_{1/2}$ = 0.35. **15e** (o = 6, m = 10): Anal. found: Cl, 0.06 (n^{Cl} < 0.02). ^{19}F NMR δ −136.1, $L_{1/2}$ = 0.45.

Poly-*para*-[3-(3-fluoro-4-methoxyphenyl)propoxy]-alkoxymethylpolystyrenes (15f, 15i, Alkoxy = Butoxy and 15g, 15j, Alkoxy = Nonoxy). 13f (m = 10): Anal. found:

Cl, 0.03 (n^{Cl} < 0.01). ^{19}F NMR δ −136.1, $L_{1/2}$ = = 0.85. **15i** (m = 10): Anal. found: Cl, 0.05 (n^{Cl} < 0.02). ^{19}F NMR δ −136.0, $L_{1/2}$ = 0.65. **15g** (m = 15): Anal. found: Cl, 0.13 (n^{Cl} < 0.04). ^{19}F NMR δ −135.9, $L_{1/2}$ = 1.35. **15j** (m = 15): Anal. found: Cl, 0.06 (n^{Cl} < 0.02). ^{19}F NMR δ −136.0, $L_{1/2}$ = 1.05.

Poly-*para*-[3-(3-fluoro-4-methoxyphenyl)propoxymethyl]polystyrenes (15a, 15h). 15a (m = 5): Anal. found: Cl, 0.02 (n^{Cl} < 0.01). ^{19}F NMR δ −135.9, $L_{1/2}$ = 1.00. ^{13}C NMR δ 152.5 (d, $^1J_{C-F}$ = 220.0), 146.0, 135.6, 124.3, 116.6, 113.8, 73.3 (matrix), 69.6, 56.7 (OMe), 40.9 (matrix), 31.9. **15h** (m = 5): Anal. found: Cl, 0.04 (n^{Cl} = 0.01). ^{19}F NMR δ −135.9, $L_{1/2}$ = 0.60.

Poly-*para*-(*N*-*tert*-butoxycarbonylpyrrolidin-2(*S*)-ylmethoxymethyl)polystyrene (21b). IR ν (cm^{-1}) 1700. Anal. found: Cl <0.1 (n^{Cl} <0.02).

Cleavage of Methoxy Group. General Procedure. A slurry of the requisite resin (**15a**−**j**) in anhydrous DMF (8−10 mL/g of polymer) is stirred slowly in a Schlenck tube to obtain an homogeneous swelling. A freshly prepared 10^{-3} M solution of sodium ethanethiolate in DMF (6−8 equiv) is then added dropwise under nitrogen pressure at room temperature. The reaction mixture is heated to 100 °C for 24 h, and the reaction is monitored by gel-phase ^{19}F NMR spectrometry. The mixture is cooled to room temperature, MeOH is added (6−8 mL/g of resin), and the resin is neutralized by adding a 5×10^{-3} M solution of H_2SO_4 (6−8 mL/g of polymer). The mixture is stirred for an additional 30 min, and the resultant resin is filtered and sequentially washed with EtOH, THF, and ether (15−20 mL of each solvent/g of polymer). The resin thus obtained is dried in a warming desiccator under reduced pressure (40 °C/20 mbar).

Poly-*meta*,*para*-[3-(3-fluoro-4-hydroxyphenyl)propoxy]-alkylpolystyrenes (16b−e) (Alkyl = *n*-Propyl, *n*-Butyl, *n*-Pentyl or *n*-Hexyl, *o* = 3, 4, 5 or 6, Respectively). IR ν 3300. **16b** (o = 3, m = 7): ^{19}F NMR δ −140.6, $L_{1/2}$ = 0.80 ppm. **16c** (o = 4, m = 8): ^{19}F NMR δ −140.4, $L_{1/2}$ = 1.05 ppm. **16d** (o = 5, m = 9): ^{19}F NMR δ −140.5, $L_{1/2}$ = 0.80 ppm. **16e** (o = 6, m = 10): ^{19}F NMR δ −140.4, $L_{1/2}$ = 1.15 ppm.

Poly-*para*-[3-(3-fluoro-4-hydroxyphenyl)propoxy]alkoxymethylpolystyrenes (16f and 16i, Alkoxy = Butoxy and 16g, 16j, Alkoxy = Nonoxy). IR ν 3300. **16f** (m = 10): ^{19}F NMR δ −139.5, $L_{1/2}$ = 2.05 ppm. **16i** (m = 10): ^{19}F NMR δ −140.7, $L_{1/2}$ = 1.50 ppm. **16g** (m = 15): ^{19}F NMR δ −141.2, $L_{1/2}$ = 2.30 ppm. **16j** (m = 15): ^{19}F NMR δ −139.5, $L_{1/2}$ = 1.95 ppm.

Poly-*para*-[3-(3-fluoro-4-hydroxyphenyl)propoxymethyl]polystyrenes (16a, 16h). IR ν 3300. **16a** (m = 5): ^{19}F NMR δ −139.6, $L_{1/2}$ = 1.60 ppm. ^{13}C NMR δ 151.4 (d, $^1J_{C-F}$ = 228.0), 142.2, 134.8, 124.8, 117.8, 116.0, 69.9, 31.8. **16h** (m = 5): ^{19}F NMR δ −139.4, $L_{1/2}$ = 1.40 ppm.

2-(*S*)-(*ortho*-fluorophenoxymethyl)-*N*-*tert*-butoxycarbonylpyrrolidine (20a). To a mixture of *ortho*-fluorophenol (**19**) (3.5 mL, 40 mmol), *N*-BOC-prolinol **1c** (12.0 g, 60 mmol, 1.5 equiv) and PPh_3 (15.7 g, 60 mmol, 1.5 equiv) in anhydrous THF (150 mL) are added dropwise under nitrogen diisopropylazodicarboxylate (DIAD, 11.6 mL, 60 mmol, 1.5 equiv). The resultant mixture is stirred for 6 h at room temperature and evaporated. The crude product is diluted with *tert*-butyl methyl ether (50 mL) to precipitate triphenylphosphine oxide. Filtration and evaporation of the filtrate delivers a crude product, which is purified by flash chromatography on silica and eluted with a 6:4 mixture of *n*-pentane/ether to afford 10 g (85%) of the desired amine **20a** as a colorless oil. $[\alpha]_{DD}^{25}$ = 56.75° (c = 2; $CHCl_3$). ^{1}H NMR δ 7.02−6.84 (m, 4 H), 4.14 (m, 2 H), 4.01 (m, 1 H), 3.39 (m, 2 H), 2.03 (m, 2 H), 1.85 (m, 2 H), 1.43 (s, 9 H). ^{19}F NMR (282 MHz) δ −134.35 (s, 0.5 F), −135.50 (s, 0.5 F). ^{13}C NMR δ 155.98 and 155.68, 154.03 and 153.89 (d, $^1J_{C-F}$ = 246.5), 147.25 (m), 125.39, 122.43 and 121.98 (d, $^3J_{C-F}$ = 5.3) 117.27 and 117.06 (d, $^2J_{C-F}$ = 10.4), 116.19 and 115.97, 80.00 and 79.61, 70.12 and 69.36, 56.30, 47.33 and 46.92, 29.04 and 28.32, 28.79, 24.13 and 23.13. Duplicate signals are due to the presence of two rotamers. MS (EI) m/z (rel int.) 295 ($M^{+\bullet}$), 222 (−O*t*-Bu, 22), 170 (26), 114 (60), 70 (100), 57 (76). IR (KBr) ν 1742, 1690. Anal. Calcd for $C_{16}H_{22}FNO_3$: C, 65.07; H, 7.51; N, 4.74. Found: C, 65.23; H, 7.42; N, 4.78.

Mitsunobu Coupling. General Procedure. The requisite resin (**16a**−**j**), PPh_3 (3 equiv per mol of ArOH units), *N*-BOC-prolinol **1c** (3 equiv), and anhydrous THF (15 mL/g of polymer) are sequentially placed in a Schlenck tube under nitrogen, and the resultant heterogeneous mixture is stirred at room temperature for 10 min. DIAD (3 equiv) is then added dropwise while keeping the temperature at 25 °C. The mixture is stirred for 3 days, and the reaction is monitored by gel-phase ^{19}F NMR spectrometry. After completion, acetone is added to the reaction mixture and stirring is continued for an additional 30 min. The polymer is filtered and sequentially washed with acetone, EtOH, and THF (30−50 mL of each solvent/g of polymer). The resin is dried in a warming desiccator under reduced pressure (40 °C/20 mbar).

Poly-*meta*,*para*-{3-[3-fluoro-4-(*N*-*tert*-butoxycarbonylpyrrolidin-2-(*S*)-ylmethoxy)phenyl]propoxy}alkylpolystyrenes (17b−e) (Alkyl = *n*-Propyl, *n*-Butyl, *n*-Pentyl or *n*-Hexyl, *o* = 3, 4, 5 or 6, Respectively). IR ν 3300, 1700. **17b** (o = 3, m = 7): T_{NMR} = 88%.[29] and T_{Ana} = 85%. Anal. found: N, 1.16 (n^N = 0.83); F, 1.86 (n^F = 0.98). ^{19}F NMR δ −135.1 (d, 0.88F), $L_{1/2}$ = 1.25, −140.3 (s, 0.12F). **17c** (o = 4, m = 8): T_{NMR}= 91% and T_{Ana}= 93%. Anal. found: N, 1.51 (n^N = 1.08); F, 2.20 (n^F = 1.16). ^{19}F NMR δ −135.1 (d, 0.91F), $L_{1/2}$ = 1.30, −140.0 (s, 0.09F). **17d** (o = 5, m = 9): T_{NMR} = 78% and T_{Ana} = 76%. Anal. found: N, 1.12 (n^N = 0.80); F, 2.00 (n^F = 1.05). ^{19}F NMR δ −135.0 (d, 0.90F), $L_{1/2}$ = 1.30, −139.9 (s, 0.10F). **17e** (o = 6, m = 10): T_{NMR} = 90% and T_{Ana} = 90%. Anal. found: N, 1.30 (n^N = 0.93); F, 1.96 (n^F = 1.03). ^{19}F NMR δ −135.1 (d, 0.90F), $L_{1/2}$ = 1.40, −139.9 (s, 0.10F).

Poly-*para*-{3-[3-fluoro-4-(*N*-*tert*-butoxycarbonylpyrrolidin-2-(*S*)-ylmethoxy)phenyl]propoxy}alkoxymethylpolystyrenes (17f, 17i, Alkoxy = Butoxy and 17g−j, Alkoxy = Nonoxy). $T_{NMR} \approx T_{Ana} \approx$ 100%. IR ν 1700. **17f** (m = 10): Anal. found: N, 1.39 (n^N = 0.99); F, 1.94 (n^F = 1.02). ^{19}F NMR δ −135.2, $L_{1/2}$ = 2.05. **17i** (m = 10): Anal. found: N, 0.56 (n^N = 0.40); F, 0.75 (n^F = 0.39). ^{19}F NMR δ −134.8, $L_{1/2}$ = 1.65. **17g** (m = 15): Anal. found: N, 0.88

($n^N = 0.63$); F, 1.05 ($n^F = 0.55$). ^{19}F NMR δ −135.3, $L_{1/2}$ = 2.15. **17j** (m = 15): Anal. found: N, 0.18 ($n^N = 0.13$); F, 0.29 ($n^F = 0.15$). ^{19}F NMR δ −135.0, $L_{1/2}$ = 1.95.

Poly-*para*-{3-[3-fluoro-4-(*N*-*tert*-butoxycarbonylpyrrolidin-2-(*S*)-ylmethoxy)phenyl]propoxymethylpolystyrenes (17a, 17h). $T_{NMR} \approx T_{Ana} \approx 100\%$. IR ν 1700. **17a** (m = 5): Anal. found: N, 1.54 ($n^N = 1.12$); F, 2.15 (n^F = 1.13). ^{19}F NMR δ −134.8, $L_{1/2}$ = 2.25. ^{13}C NMR δ 153.4 (d, $^1J_{C-F}$ = 243.8), 145.4, 135.9, 124.3, 116.8, 115.6, 79.8, 69.7, 69.6, 56.4, 47.4, 31.9, 29.0. **17h** (m = 5): Anal. found: N, 0.73 ($n^N = 0.52$); F, 0.99 ($n^F = 0.52$). ^{19}F NMR δ −135.2, $L_{1/2}$ = 1.65.

2-(*S*)-(*ortho*-Fluorophenoxymethyl)pyrrolidine (20b). Trifluoroacetic acid (5 mL, 65 mmol, 2 equiv) is added to a solution of **20a** (10 g, 33 mmol, 1 equiv) in CH_2Cl_2 (45 mL) at room temperature under nitrogen. The mixture is stirred for 4 h at the same temperature, after which a saturated aqueous solution of potassium carbonate (40 mL) is added. The organic layer is separated, washed with water (2 × 20 mL), dried over $MgSO_4$, and concentrated. Kugelrohr distillation under reduced pressure (130 °C/0.8 mbar) gives the product as a yellow oil (6.0 g, 93%). $[\alpha]_D^{25} = -2.25°$ (c = 2; $CHCl_3$). ^{1}H NMR (300 MHz) δ 6.99−6.79 (m, 4 H), 3.86 (m, 2 H), 3.44 (m, 1 H), 2.95 (m, 1 H), 2.86 (m, 1 H), 2.74 (s, 1 H), 1.84 (m, 1 H), 1.70 (m, 2 H), 1.49 (m, 1 H). ^{19}F NMR δ −135.04 (m, 1F). ^{13}C NMR δ 153.00 (d, $^1J_{C-F}$ = 244.5), 147.39 (d, $^2J_{C-F}$ = 10.5), 124.55 (d, $^3J_{C-F}$ = 3.5), 121.36 (d, $^3J_{C-F}$ = 6.3), 116.34 (d, $^2J_{C-F}$ = 18.3), 115.36, 72.98, 57.45, 46.78, 28.18, 25.49. MS (EI) *m*/*z* (rel int.) 196 ($M^+ + 1$, 16), 180 (4), 166 ($M^+ - F$, 3), 112 (11), 95 (8), 83 (15), 70 (100). IR (KBr) ν 3300, 1690, 1610, 1590. Anal. Calcd for $C_{11}H_{14}FNO$: C, 67.67; H, 7.23; N, 7.17. Found: C, 67.79; H, 7.24; N, 7.13.

Cleavage of the *tert*-Butoxycarbonyl Group. General Procedure for Resins 18. The requisite polymer (**17a**−**j**) is swollen in anhydrous CH_2Cl_2 (15−20 mL/g of polymer), and TFA (1.5−2.0 mL/g of polymer, 8−10 equiv) is added under nitrogen. The mixture is stirred at room temperature for 12 h. The resin is filtered and stirred in the Schlenck tube with a 2:2:1 mixture of MeOH/H_2O/NEt_3 (10−15 mL/g of polymer) for 30 min. Filtration; sequential washing with EtOH, THF, and ether (15−20 mL of each solvent/g of polymer); and drying in a warming desiccator under reduced pressure (40 °C/20 mbar) delivers the unprotected supported amines **18**.

Poly-*para*-{3-[3-fluoro-4-(pyrrolidin-2-(*S*)-ylmethoxy)-phenyl]propoxy}alkoxymethylpolystyrenes (18f, 18i) (Alkoxy = Butoxy). Reaction is quantitative. (**18g, 18j**) (alkoxy = nonoxy). Action of TFA was destructive. **18f**, **18i**: IR ν 3350. **18f** Anal. found: N, 1.58 ($n^N = 1.13$); F, 2.33 ($n^F = 1.22$). ^{19}F NMR δ −135.0, $L_{1/2}$ = 1.25. **18i**. Anal. found: N, 0.57 ($n^N = 0.41$); F, 0.86 ($n^F = 0.45$). ^{19}F NMR δ −134.8, $L_{1/2}$ = 2.25. **18g**. Anal. found: N, 1.06 (n^N = 0.71); F, 2.73 ($n^F = 0.38$). ^{19}F NMR δ −136.0, $L_{1/2}$ = 2.85. **18j**. Anal. found: N, 0.07 ($n^N = 0.05$); F, 0.32 ($n^F = 0.17$). ^{19}F NMR δ −136.0, $L_{1/2}$ = 3.05.

Poly-*meta*,*para*-{3-[3-fluoro-4-(pyrrolidin-2-(*S*)-ylmethoxy)phenyl]propoxy}alkylpolystyrenes (18b−e) (Alkyl = *n*-Propyl, *n*-Butyl, *n*-Pentyl or *n*-Hexyl, *o* = 3, 4, 5 or 6, Respectively). 18b: IR ν 3350. Anal. found: N, 1.22 ($n^N = 0.87$); F, 1.96 ($n^F = 1.03$). ^{19}F NMR δ −135.0, $L_{1/2}$ = 0.85. **18c**: IR ν 3350. Anal. found: N, 1.62 ($n^N = 1.16$); F, 2.38 ($n^F = 1.25$). ^{19}F NMR δ −135.0, $L_{1/2}$ = 0.90. **18d**. Anal. found: N, 1.24 ($n^N = 0.89$); F, 2.05 ($n^F = 1.08$). ^{19}F NMR δ −135.0, $L_{1/2}$ = 1.10. **18e**. Anal. found: N, 1.48 (n^N = 1.06); F, 2.26 ($n^F = 1.19$). ^{19}F NMR δ −135.0, $L_{1/2}$ = 1.05.

Poly-*para*-{3-[3-fluoro-4-(pyrrolidin-2-(*S*)-ylmethoxy)-phenyl]propoxymethyl}polystyrenes (18a, 18h). IR ν 3350. **18a** (n = 5): Anal. found: N, 1.68 ($n^N = 1.20$); F, 2.24 (n^F = 1.18). ^{19}F NMR δ −134.9, $L_{1/2}$ = 1.60. **18h** (n = 5) Anal. found: N, 0.76 ($n^N = 0.54$); F, 1.06 ($n^F = 0.56$). ^{19}F NMR δ −135.1, $L_{1/2}$ = 1.50.

Poly-*para*-(pyrrolidin-2-(*S*)-ylmethoxymethyl)polystyrene (21c). Resin **21b** (10 g) and anhydrous CH_2Cl_2 (50 mL) are placed in a Schlenck reactor at room temperature and gently stirred (regular magnetic stirring). After 10 min, trifluoroacetic acid (50 mL) is added under nitrogen, and the slurry is refluxed for 6 h. The mixture is cooled and filtered, and the resin thereby obtained is introduced in a second Schlenck reactor along with methanol (40 mL), water (40 mL), and triethylamine (20 mL). The slurry is stirred at room temperature for 0.5 h. Filtration; sequential washing of the polymer with ethanol (100 mL), distilled THF (100 mL), and distilled ether (100 mL); and drying under vacuum (20 mbar) delivers the supported chiral amine **21c**. IR ν 3350. Anal. found: N, 1.50 ($n^N = 1.07$); Cl, <0.10.

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(22) Under the conditions defined in the Experimental Section, supported chiral amine **21a** was reproducibly obtained in 89% yield, based on elemental analysis (% N = 1.94; % Cl = 1.22). Similarly, the unreacted chloromethylene units were reduced with $LiEt_3BH$ to afford a material containing <0.05% Cl by elemental analysis.

(23) These results thus translate into resins possessing 81−87% of supported amine units and 19−13% of phenol units (entries 2, 4, and 5 of Table 7).

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(28) $L_{1/2}$: half-height width reported in parts per million.

(29) T_{NMR} was calculated by relative integration of both peaks in the ^{19}F NMR spectrum.

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